# Synopsis for Registration as Research Student

# For

# Doctoral Degree

# On

# Retinal Image Characterization for Disease Detection and Diagnosis

## By

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# 1. Introduction and Motivation

Diabetes Mellitus is a metabolic disorder, characterized by hyperglycemia in which there is an excess of glucose circulating in the blood. It is also commonly known as diabetes. Insulin is the hormone secreted by pancreas responsible for maintaining blood glucose level in the body. The pancreas of the person affected with diabetes either cannot produce enough insulin, utilizes it incorrectly or both. Insulin helps the body to utilize glucose from carbohydrates in the food and facilitates it to enter into body cells for getting burned to attain energy. The body normally regulates blood glucose delicately in the fasting state in a range around 4 to 5.5 mmol/L in the plasma. Insulin helps in preventing blood glucose level from getting too high (hyperglycemia) or too low (hypoglycemia).

Hyperglycemia leads to excessive glycosylation of proteins, and this is the primary attribute of the long-term complications of diabetes. Diabetes is usually divided into two categories i.e. 'Type – I diabetes' and 'Type – II diabetes'. Type – I diabetes is characterized by the inadequacy of insulin and Type – II diabetes has attributes showing the pertinent inadequacy of insulin corresponding to insulin resistance. Insulin insufficiency – either complete or partial – is the fundamental component behind diabetes. However, different variables have an impact and can be more critical while considering treatment.

Insulin requirement depends upon a complex balance between various hormones, existing energy stores, physical activity, and resistance to insulin action in muscle, liver and adipose tissue [1]. Modern lifestyle in the developing world has significantly reduced physical activity, and people tend to have an intake of high-calorie food which results in an imbalance of energy that further leads to greater obesity, insulin resistance, and Type – II diabetes. Insulin resistance is defined as the downgraded capacity of peripheral tissues and the liver to respond to insulin. This insulin resistance is frequently found in diabetes and is particularly critical in Type – II diabetes where it aggravates the secretory deformities [2]. A person with diabetes has high blood glucose either because they are not producing enough insulin, or because the body does not respond appropriately to insulin.

Diabetes is considered the world's one of the biggest health emergencies of the 21$^{st}$ century. A number of people living with this condition are progressively increasing each year. According to an estimate of International Diabetes Federation [3], there are now 415 million people aged between 20 to 79 with diabetes worldwide. IDF estimated a further 318 million individuals with impaired glucose tolerance, which gradually increases the risk of developing the disease in the future. Also, the majority of individuals with diabetes are from developing countries like China (109 million) and India (69.2 million).

Both Type – I and Type – II diabetes are linked with long-term microvascular complications like retinopathy, nephropathy, and neuropathy. Consistent high blood glucose concentration also leads to macrovascular complications such as heart failure, stroke, disease, and peripheral vascular disease. Other health problems also continue to occur due to glycation such as diabetic foot, osteoporosis, cheiroarthropathy, and cataract. In particular diabetic retinopathy was

considered as a diabetes-related health issue that research studies anticipated the time span amongst advancement and diagnosis of diabetes by backward linear regression [1].

According to a recent survey conducted by World Health Organization (WHO), healthcare costs associated with the treatment of health issues due to diabetes amounts to approximately US$ 825 billion dollars per year [4]. Diabetes is globally significant and costly complication, and its prevalence is growing at almost epidemic levels. Furthermore, diabetic patients encounter significant decrements in daily activities and quality of life with increasing visual impairment. Hence, novel and innovative ways of identification, diagnosis, treatment and follow-up are essential in the management of this growing problem.

The most eloquent indicator of the pervasiveness of diabetic retinopathy is a span of diabetes. Given the significance of diabetic retinopathy and its impact on retina creating a visual deficiency, and also its utility in giving a window on the history of diabetes in the individuals, this chapter will concentrate on definition and classification of diabetic retinopathy, the epidemiology, automatic screening of retina by computer aided diagnosis and teleophthalmology tools.

## 2. Literature Survey

**Exudate Detection:** Automatic detection of exudates is a challenging issue, since the retinal fundus images often have uneven illumination and are poorly contrasted. Under these complex conditions, several related exudate detection methods have been proposed, which can be divided into the following four categories: (1) thresholding-based [5]–[7], (2) region growing-based [8], [9], (3) morphological-based [10]–[12], and (4) pixel-based classification [13]–[17]. Thresholding analysis can be regarded as the simplest manner to segment exudates from other lesions in retinal images. In region growing segmentation-based algorithms, the characteristic of spatial gray-level contiguity was used to segment retinal images or combined edge detection for exudate extraction. However, region growing is time-consuming. In morphological operators different structuring elements are used for exudate candidate extraction.

**Micro-aneurysms detection:** The earliest microaneurysm (MA) detection method was proposed by [18]. They used mathematical morphology approach to detect the microaneurysms in fluorescein angiogram. Two variants of morphological top-hat transformation methods for extracting MAs within fluorescein angiograms were developed by [19] and [20]. In [21], a local template matching in the wavelet domain has been used for detecting MAs. In addition, [22] employed Multi-scale Gaussian Correlation Coefficients (MSCF) method to detect MAs. [23] presented a hybrid scheme which combined morphological top-hat transform with a KNN classifier for MA detection. After that [24] proposed an approach which integrated the Gaussian mixture model with a logistic regression classification into a unified framework for MA detection. Furthermore, [25] developed a MA detection method, which combined the Dictionary Learning (DL) with Sparse Representation Classification (SRC).

**Hemorrhage Detection:** Hemorrhages and micro-aneurysms are mostly detected together and associated with a single label. In previous works, approaches based on morphological operations [26], wavelet operations [27] and manual designed features in combination with

statistical classifiers [28]–[31] were used for the detection of hemorrhages and micro-aneurysms. Although hemorrhages are different in size and shape and pose different clinical relevance, only few works have addressed the identification of hemorrhages separately on color fundus images [32], [33].

**Vessel Segmentation and Diameter Measurement:** Several retinal vessel detection methods have been proposed earlier and are present in the literature. [34] used an inpainting filter which inpaint exudates and multi-scale Hessian approach for retinal vessel enhancement. [35] used region growing approach by histerisis thresholding in combination with response vector similarity of adjacent pixels. [36] selects nodes from the Max-Tree and then these nodes are classified using baysian classifer using hierarchical Markovian model. Vessel diameter measurement is done by [37].

**Fovea and Optic Disc Detection:** [38] have utilized Principal Component Analysis (PCA) and modified Active Shape Model (ASM) for localizing OD and BV. The position of macula is obtained using ASM and parabola fitting at geometrical distance. [39] have removed the BVs and using an appropriate threshold, detected the OD. From the ROI, the dark intensity pixels are segmented by setting a threshold. [40] have detected the OD using PCA. The BV are later removed so that their intensity does not interfere with the macula detection. The OD is obtained using HSI image. The BV are removed prior to macula detection. The macula region is then obtained by setting an appropriate threshold. [41] have determined the OD location using PCA.

**Automated identification of diabetic retinopathy stages:** The main stages of diabetic retinopathy are non-proliferative diabetic retinopathy and proliferative diabetic retinopathy. [42] proposed a computer based approach for detection of diabetic retinopathy stage using fundus images. They used morphological processing techniques and texture analysis methods on the fundus images to detect the features such as area of hard exudates, area of the blood vessels and the contrast. Their protocol uses total of 140 subjects consisting of two stages of DR and normal. Their extracted features were found statistically significant with distinct mean and SD. These features are then used as an input to the artificial neural network for an automatic classification.

**Grading the Severity of Diabetic Macular Edema Cases:** Welfer et al [43] introduced a new computer based scheme for detecting and grading Diabetic Macular Edema (DME) signs using color eye fundus images. DME has three severity levels, namely: (1) DME mild; (2) DME moderate; (3) DME severe based on distribution of exudates in macular region. They have done grading of the diabetic macular edema in color eye fundus images by efficiently locating the fovea and the optic disc, and then the spatial distribution of exudates is evaluated around the fovea center. This exudate distribution is analysed based on the retinal sectors (retinal image is subdivided in 10 subfields). In order to determine the decision boundaries between the different classes (i.e. thresholds), the classification and regression tree method is used (CART). Their grading scheme was trained using smoothed bootstrap samples and fundus images which are not in the training set were used for testing.

## 3. Identified open Research Problems

Diabetic retinopathy is a progressive disease. So for detection of abnormal features accurate detection of normal features is essential to avoid false positives. Hence following are the identified research problems.

1. Detection of Normal features such as Optic Disc, Retinal Vasculature, Macula, Fovea.
2. Detection of vessel diameter for the identification of diseases such as store, hypertention.
3. Detection of Abnormal features such as Microaneurysms (< 60 µm), Dot-hemorrhages, Hard exudates, Blotchy hemorrhages, Intraretinal microvascular abnormalities (IRMAs), Venous beading, Cotton wool spots, New vessels on or within one disc diameter of the disc (NVD), New vessels elsewhere (NVE), Preretinal haemorrhage, Vitreous haemorrhage, Clinically significant macular edema (CSME)
4. Grading the Severity of Diabetic Macular Edema Cases.
5. Automated identification of diabetic retinopathy stages.
6. Detection of irregularly shaped hemorrhages; Exudates and differentiating them into hard Exudates and soft exudates.

## 4. Problem Definition

The main objective of the work will be to contribute novel methods for detecting retinal vessels, macula, optic disc, diabetic macular edema etc. in the color retinal images of DR screening programs. This research will be a part of development of a DR detection system. A system for computer aided diagnosis of the retina can either decide between disease and non-disease, i.e., diagnosis or screening, or can decide the progression of disease in the same patient between two time points, i.e., progression measurement or staging.

## 5. Methodology

- Software: MATLAB and Python.
- Datasets: Numerous datasets are identified through survey which can be utilized in research are categorised for specific purposes as follows:
  - DR and DME Severity: Kaggle, MESSIDOR and IDRiD
  - DR Lesion Detection: DIARETDB1, E-Optha, HEIMED
  - AMD: ARIA, STARE
  - Optic Disc and Fovea Location: IDRiD
  - Vessel Segmentation: DRIVE, STARE
  - A/V Ratio: VICVAR
  - Vessel Width Estimation: REVIEW

## 6. Evaluation

Evaluation methods in literature suggest classification into 3 approaches: pixel-based, lesion-based, and image-based. The ROC-based analysis perfectly suits to medical decision making, being the acknowledged methodology in medical research. An evaluation protocol based on the ROC analysis is for image-based (patient-wise) evaluation and benchmarking. In clinical medicine, the terms sensitivity (SN) and specificity (SP) defined in the range [0%, 100%] or [0, 1] are used to compare methods and laboratory assessments. The sensitivity depends on the diseased population whereas the specificity on the healthy population, defined by true positive (TP), true negative (TN), false positive (FP), and false negative (FN). The x − axis of an ROC curve is 1 − specificity, whereas the y – axis represents directly the sensitivity.

## 7. Conclusion

The previous results from literature show that retinal lesion detection is a challenging task for both the automatic methods as well as the human expert. Also there is room for improvement as the best performing system does not reach the performance of the human expert. Hence, Development of systems to automate DR screening have received a lot of attention from the research community and this work will add up to their efforts to increase performance.

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